DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 81N-0060]

Orally Administered Drug Products for the Treatment of Fever Blisters for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) orally administered drug products for the treatment of fever blisters are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by August 16, 1985. New data by June 17, 1986. Comments on the new data by August 18, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by October 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of January 5, 1982 (47 FR 502), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC orally administered drug products for the treatment of fever blisters, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, two physicians submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 357, Subpart H (21 CFR Part 357, Subpart H), FDA states for the first time its position on the establishment of a monograph for OTC orally adminstered drug products for the treatment of fever blisters. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC orally administered drug products for the treatment of fever blisters.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC orally administered drug products for the treatment of fever blisters, based on the comments received and the agency's independent evaluation of the Panel's report.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the Federal Register of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III clasification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products sugject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earlies possible date.

In the advance notice of proposed rulemaking for OTC orally administered drug products for the treatment of fever blisters (published in the Federal Register of January 5, 1982; 47 FR 502), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the Federal Register. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency

has determined that is is impractical to expect new labeling to be in effect 6 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disuption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

In the event that new data submitted to the agency during the allotted 12-month comment and new data period are not sufficient to establish "monograph conditions" for OTC orally adminstered drug products for the treatment of fever blisters, the final rule will declare these products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which new drug applications approved under section 505 of the act and 21 CFR Part 314 are required for marketing. Such rule will also declare that in the absence of an approved new drug application, these products would be misbranded under section 502 of the act. The rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in Part 357.

I. The Agency's Tentative Conclusions on the Comments

Two comments from physicians concurred with the Panel's recommendations regarding the Category III status of drug product ingredients used in the treatment of fever blisters. One physician stated that although there have been various isolated reports of success in treating patients with lysine, there is a need for a double-blind study with substantial numbers of patients, adequate documentation, and careful observation for subtle differences between the control group and the lysine-treated group.

In the other comment, a physician presented a brief summary of results obtained from using lysine tablets in about 7 to 10 cases of frequent recurrent herpes simplex and from using a product containing *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*. Some patients thought that the lysine tablets reduced the recurrence rate; others thought the tablets useless. In reference to the *Lactobacillus acidophilus-Lactobacillus bulgaricus* product, the physician stated that this product was rarely used and then only in cases of chronic aphthous stomatitis (canker sore) over a prolonged period of time. The physician concluded that the results were not impressive.

The agency agrees that more data, generated from well-controlled double-blind studies, are needed to establish general recognition of safety and effectiveness for OTC orally administered active ingredients used in the treatment of fever blisters.

The Panel did not classify any of the ingredients it reviewed in Category I, but did recommend that lysine (lysine hydrochloride), *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* be classified in Category III. (See 47 FR 506.)

No new data and information in support of the safety and effectiveness of any condition reviewed by the Panel has been submitted to the agency. In this tentative final monograph the agency concurs with the Panel's recommendations; however, should data establishing the safety and effectiveness of any condition subject to this rulemaking be received during the comment and new data periods following publication of this tentative final monograph, the agency will include those conditions in the final monograph.

II. The Agency's Tentative Adoption of the Panel's Report

Summary of Ingredient Categories and Testing of Category II and Category III Conditions

A. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's classification of these ingredients. For the convenience of the reader the following table is included as a summary of the categorization of OTC orally administered fever blister active ingredients:

Orally administered fever blister active ingredients	Panel	Agency
Lactobacillus acidophilus	III	III
Lactobacillus bulgaricus	III	III
Lysine (lysine hydrochloride)	III	III

The agency is not aware of any data demonstrating the safety and effectiveness of any ingredients not listed above when used OTC as orally administered drug products for the treatment of fever blisters, including those listed in the Panel's report at 47 FR 504, Part I, paragraph C.2. Therefore, the agency classifies all other ingredients as Category II for this use.

B. Testing of Category II and Category III conditions. The Panel recommended testing guidelines for OTC orally administered drug products for the treatment of fever blisters (47 FR 502). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any orally administered fever blister ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the

availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC orally administered drug products for the treatment of fever blisters, is a major rule.

For purposes of the Regulatory Flexibility Act, Pub. L. 96–354, the economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety and efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC orally administered drug products for the treatment of fever blisters. Comments regarding the economic impact of this rulemaking should be accompanied by appropriate documentation.

The agency previously invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC orally administered drug products for the treatment of fever blisters. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submittee by October 15, 1985. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) (April 26, 1985; 50 FR 16636) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Exclusivity of Labeling

In the **Federal Register** of April 22, 1985 (50 FR 15810), the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under this policy, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph.

The proposed rule would establish three alternatives for stating the indications for use in OTC drug labeling while all other aspects of OTC drug labeling (i.e., statement of identity, warnings, and directions for use) would continue to be subject to the existing exclusivity policy. The proposed rule for OTC orally administered drug products for the treatment of fever blisters included in this document incorporates the exclusivity proposal by providing for the use of other truthful or nonmisleading statements in the product's labeling to describe the indications for use. After considering all comments submitted on the proposed revision to the exclusivity rule, the agency will announce its final decision on this matter in a future issue of the **Federal Register.** The final rule for OTC orally administered drug products for the treatment of fever blisters will incorporate the final decision on exclusivity of labeling.

Interested persons may, on or before August 16, 1985 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before October 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before June 17, 1985, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before August 18, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 18, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 357

OTC drugs; anthelmintic drug products, cholecystokinetic drug products, deodorant drug products for internal use, orally administered drug products for fever blisters, poison treatment drug products, and smoking deterrent drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 by adding new Subpart H, to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

* * * * *

Subpart H—Orally Administered Drug Products for the Treatment of Fever Blisters

Sec.

357.701 Scope.
357.703 Definitions.
357.710 Orally administered active ingredients for the treatment of fever blisters. [Reserved]
357.750 Labeling of orally administered drug products for the treatment of fever blisters.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); (5 U.S.C. 553); 21 CFR 5.11.

Subpart H—Orally Administered Drug Products for the Treatment of Fever Blisters

§ 357.701 Scope.

(a) An over-the-counter drug product for the treatment of fever blisters in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.703 Definitions.

As used in this subpart:

(a) *Fever blisters.* Recurrent sores on the lips and other areas around the mouth, usually caused by herpes simplex virus, Type I. Characterized by local tissues swelling followed by inflammation, the sores evolve into vesicular eruptions and then crust and fade.

(b) *Cold sores.* Fever blisters.

§ 357.710 Orally administered active ingredients for the treatment of fever blisters. [Reserved]

§ 357.750 Labeling of orally administered drug products for the treatment of fever blisters.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "fever blister treatment."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of the discomfort of fever blisters (cold sores)." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce of unapproved new drugs.

(c) *Warnings.* The warning required by § 330.1(g) concerning overdoses is not required on orally administered active ingredients for the treatment of fever blisters.

(d) *Directions.* [Reserved].

Frank E. Young,

Commissioner of Food and Drugs.

Dated: May 6, 1985.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85–14440 Filed 6–14–85; 8:45 am]
BILLING CODE 4160–01–M